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DANCE ROUND

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.
Robert Frost

HOMO DIABESUS: INVOLVEMENT OF METABOTROPHIC FACTORS

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Abstract

Diabesity is a new term which refers to type 2 diabetes mellitus and obesity found in one individual, hence *Homo diabesus.* Previously we presented our hypothesis of metabotrophic factors (MTF), also termed metabotrophins. Onward we described *Homo obesus* (man obese) as a metabotrophin-deficient species. Now - as a phenotypic variety of this species - we introduce *H. diabesus*. Endogenous MTF are in general signaling proteins able to improve cardiovascular and metabolic homeostasis including that of lipids, glucose, energy, inflammation, angiogenesis, and cognition. Hence pharmacological manipulations of the secretion and/or signaling of MTF might bring a therapeutic benefit for *H. diabesus*. Here we *Dance Round* the hypothesis that deficit and/or dysfunction of MTF may lead to diabesity. Arguably, an updated list of MTF including nerve growth factor, brain-derived neurotrophic factor, adiponectin, humanin, irisin and other adipose- and nonadipose-derived bioactive molecules is presented. Overall this may cultivate a novel pathogenic and therapeutic thinking for cardiometabolic disease.

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Key words: type 2 diabetes, obesity, adipokines, NGF, BDNF, metabotrophins, cardiometabolic disease

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Introduction

Today, the most widespread disease around the world is not AIDS or malaria or any other transmissible disease - it is obesity, the major global disease, *globesity*. Although the pathogenesis is not yet completely understood, there is now solid evidence that type 2 diabetes mellitus is a disease of the obese man (*Homo obesus*) (1). New clinical trials demonstrate that as little as 5% body weight loss is sufficient to prevent most obese subjects with impaired glucose tolerance developing type 2 diabetes. Since type 2 diabetes is obesity dependent, the term *diabesity* was adopted (2,3), and herein *Homo diabesus* is introduced.

Adipose tissue: the Renaissance of a seemingly ubiquitous tissue

One of biggest recent achievements in studying cardiovascular and metabolic diseases (atherosclerosis, hypertension, obesity, type 2 diabetes, metabolic syndrome, and Alzheimer's disease) is associated with the "rediscovery" of a neglected tissue, the adipose tissue.

Adipose tissue considered as passive storage-release of lipids by most

cell biologists and pathologists for a long period of time, can no longer be ignored in almost any biomedical field. The last 19-20 years, that is, the time after Jeffrey Friedman's discovery of leptin, have seen it rise above the horizon to take center stage in so many syndromes and diseases that it leaves most scientists and medical doctors astonished. There are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), to which were recently added *brite* (brown in white) adipose tissue; also brown adipocytes found in skeletal muscles are referred to as *bruscle* (brown in muscle) adipocytes (4). Cumulatively, such an adipocentric approach has revealed that while BAT is major thermogenic organ, WAT is the body's largest endocrine and paracrine organ producing multiple signaling proteins collectively termed adipokines (5-11), with nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) being also produced from adipose tissue (12).

Multiple life of neurotrophins

The past three decades has witnessed a number of breakthroughs in the study on Rita Levi-Montalcini's NGF, including the family of proteins termed neurotrophins (NGF, BDNF, NT3/4 alike). Studies have revealed that the neurotrophins NGF and BDNF are not only stimulating for nerve growth and survival, but also exert trophic effects over (*i*) immune cells, acting as immunotrophins, (*ii*) keratinocytes, enterocytes, prostate and breast epithelial cells, acting as epitheliotrophins, and (*iii*) endothelial cells, acting as angiogenic factors (reviewed in 13).

In 2003 we, for the first time, enriched the *NGF-ome* with one more expression, that is, metabotrophic action on glucose, lipid, energy, pancreatic beta cell and cardiovascular homeostasis, and thus, together with BDNF, designated *metabotrophins* (from Greek *metabole*, and *trophe*, nutrition, means "nutritious for metabolism") (14-16). Onward, the proof-of-hypothesis was based on results demonstrating that the circulating and/or tissue levels of NGF and BDNF are (commonly) decreased in atherosclerosis and metabolic syndrome (17,18), type 2 diabetes (19,20), depression and other psychiatric diseases (see 13), and in Alzheimer's disease which nowadays is considered as type 3 diabetes (21-23, also see Viviana Triaca's review in this volume of *Adipobiology*).

Implication of NGF and BDNF in cardiometabolic disease: results of a dream

During his student life at the Medical University, Varna, Bulgaria, one of us (GNC) used to work four years (1962-1966) as Research Associate at the Department of Pharmacology. It was that period of time when he for the first time "met" Professor Rita Levi-Montalcini, reading her papers on NGF. Since then he has being infected by this talented molecule, and thought how to reach her Institute in Rome, Italy. Although some colleagues told him that it is a very difficult pursuit, he continued to believe more in the art of dream as presented by Emily Dickinson's *To Make a Prairie* (*To make a prairie it takes a clover and one bee,/ One clover, and a bee,/…The dream alone will do,/ If bees are few.)*

On its road, in 1997 he has applied for NATO-CNR Research Fellowship, which required acceptance letter by the host institution, RLM's Institute of Neurobiology, National Research Council (CNR), Rome. Dr Luigi Aloe, Research Director of the Institute, provided such a letter, consequently awarded him the Fellowship. Thus in June 1998 GNC appeared in the Institute of Neurobiology in Rome. During this first four months there as well as almost each year further on he was pleased of common research work, producing a "paradigm shift" from neurotrophins to metabotrophins in cardiometaboic disease.

In our further research pursuit of MTF, we have, for the first time, published data of reduced circulating levels of NGF and BDNF in patients in *advanced stage* of metabolic syndrome as compared with healthy subjects (17,18). Contrary, the circulating levels of NGF and BDNF were significantly elevated in patients in *early stage* of metabolic syndrome (24). Whether the metabotrophic reserve of the organism is discharged with the progression of metabolic syndrome, remains to be elucidated.

In an attempt to "close" the metabotrophic "loop" in cardiometabolic disease, we have measured circulating levels of NGF and BDNF in patients with acute coronary syndromes, and found they are significantly reduced (25, also see 26). Another own study revealed altered levels of NGF in pancreas and brain in streptozotocin-induced diabetes (27). Recently, we found that in response to experimental stress or diabetes, the amount of NGF and BDNF was altered both in WAT and BAT (12).

Selected proof-of-metabotrophic concept examples derived from other laboratories are: (*i*) pancreatic beta cells secrete NGF and express its receptor tyrosine-kinase A (TrkA), findings being implicated in the pathogenesis of diabetes mellitus (28, also see the research article of Marcia Hiriart *et al* in this volume of *Adipobiology*), and (*ii*) mutations affecting *Bdnf* gene (encoding BDNF) in mice or *Ntr2k2* gene (encoding the high-affinity BDNF receptor TrkB) in patients are associated with hyperphagia and severe obesity (1,13 and references therein). Metabotrophic effects of NGF and BDNF are summarized in Table 1.

Conclusion and perspective

We have presented an extended version of our hypothesis of the significance of adipose and nonadipose-derived MTF in the pathogenesis of cardiovascular and metabolic diseases. In this

context, the recent discovery of (*i*) humanin, a mitochondria-derived peptide expressing neuro- and metabotrophic effect (29,30), and (*ii*) irisin, a myokine/adipokine involved in the browning of WAT (31,32), may open a further perspective for the therapy of *Homo diabesus*. Selected list of *endogenous* MTF is presented in Table 2. It may open new windows for the search of *exogenous* MTF, such as (*i*) small molecules boosting secretory and/or signaling pathways of MTF (reviewed in 1,13), and (*ii*) incretin mimetics and receptor agonists, because the insulinotropic hormone glucagon-like peptide-1 (GLP-1) and exendin-4, a GLP-1 receptor agonist, exert neuro- and metabotrophic effect (33,34).

The future challenge is therefore to cultivate a neuro-metabotrophic thinking about how we can make MTF secretion and signaling work for the benefit of human's health. This may also help *Homo diabesus* to enjoy both physical and mental quality of life**.**

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Table 1. Metabotrophic effects of NGF and BDNF*

NGF shares homology with proinsulin
NGF/BDNF are produced by pancreatic beta cells and exert insulinotropic effect
NGF/BDNF are trophic factors for pancreatic beta cells, also improve beta cell transplantation
NGF up-regulates expression of LDL receptor-related protein
NGF up-regulates expression of PPARgamma
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF improves skin and corneal wound healing
NGF may improve vascular (atheroma) wound healing
NGF rescues silent myocardial ischemia in diabetes mellitus
NGF improves diabetic erectile dysfunction
NGF and BDNF suppress food intake
Healthy lifestyle increases brain and/or circulating levels of NGF/BDNF
An atherogenic diet decreases brain BDNF levels
BDNF-deficient mice develop abnormalities similar to the metabolic syndrome
BDNF improves cognitive processes

** Modified from (13). For references see the text, also (39-42).*

Table 2. Selected list of endogenous metabotrophic factors*

Secretory proteins
NGF, BDNF, Ciliary neurtrophic factor, Neuron-derived neurotrophic factor
Adiponectin, Irisin, Humanin, Omentin, Chemerin, Apelin, Otopetrin 1
Interleukin-10, Metalothionein-I,-II, Glucagon-like peptide-1
Intracellular proteins
Sitruins, PPAR-gamma, Uncoupling protein-1 (UCP-1)

** Modified from (1). For references see the text, also (35-43).*

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